QUININE PROPHYLAXIS IN NORTHERN INDIA.

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III.—THE THEORY OF QUININE PROPHYLAXIS.

Quinine is not regarded as a true prophylactic to malaria. It does not prevent infection of the red blood-cells by the parasites, but, if given in sufficient doses and over a long enough period, it may prevent an attack of malaria in an individual who has been bitten by an infective mosquito, and allow him to carry out his normal duties.

If there were ever any real doubts on the subject these have been laid to rest as a result of the celebrated work of Yorke and Macfie already referred to. They established that in order to prevent attacks of malaria developing quinine had to be continued ten days at least after the infective bite, and they considered that quinine failed to destroy all, if any, of the sporozoites. The reason for this failure is shown by the work of Acton [31], who found that, after a single dose of ten grains of quinine, the maximum concentration of quinine in the blood was only 1 in 250,000, a very much weaker concentration than is necessary to kill off all parasites.

Warrington Yorke [32] (in collaboration with Macfie) has confirmed the work of Muhlen and Kirschbaum (1924) that quinine in concentrations considerably greater than can ever occur in the blood-stream does not in vitro destroy all the malaria parasites. He found that a mixture of simple tertian blood and of a 1 in 5,000 solution of quinine is infective after incubation at 37°C for two and a half hours. Evidence is produced to show that the susceptibility to treatment in the induced malaria is bound up with the fact that in these cases one is concerned with the treatment of primary infections. The mechanism by which a cure is obtained in malaria is considered at length and the conclusion reached that the essential factor for the production of cures is the capacity of the host to produce immune body formation in response to antigen resulting from the destruction of a considerable number of merozoites, whether due to quinine treatment or to the natural powers of the patient. If for any other reason the immune body formation is insufficient the infection is not sterilized and a relapse occurs.

The failure of treatment in chronic relapse cases is explicable on the same hypothesis. The parasites in such cases are not quinine resistant, but immune body resistant. In primary cases, on the other hand, treatment does produce a cure, firstly because the immune body normally present to some extent in the blood of all patients is augmented as the result of the
antigen formed by the action of the quinine on the parasites, and, secondly, because the parasites have not yet become immune body resistant.

Interesting though this hypothesis may be, it should be borne in mind that it is still only a hypothesis and that all the evidence adduced in its favour is indirect.

Whether we accept the hypothesis of Yorke or not, it would appear from the above that quinine prophylaxis is merely a form of early treatment given in the incubation period before there are sufficient parasites present to cause a paroxysm, and that the quinine assists the natural defences of the body.

In whatever form quinine is administered, it circulates in the blood as quinine base. It is present in the plasma, is adsorbed on to the surface of the erythrocytes, but not within them. Hence such parasites as may have become intracellular escape its action. When the infected red cells burst, setting free in the blood plasma swarms of little merozoites, these merozoites attach themselves to fresh red blood-corpuscles to initiate again the schizogony cycle. The malaria parasites are therefore extra-cellular in their earlier trophozoite phase. Most malariologists, however, affirm that early in the process of development the trophozoite penetrates into the interior of the cell, and that both the schizont and gametocyte are intracellular.

M. Rowley-Lawson does not agree, and in a series of papers (1912-1919), beautifully illustrated, she maintains the view that the parasites are extra-cellular throughout the whole of the cycle in their human host, and that they wander about in the blood-stream from one blood-cell to another, applying themselves to the surface of the cells, but never penetrating into them.

Stephens and Gordon [33] hold similar views and, as a result of their studies on the relationship of the crescent to the erythrocytes, formed the opinion that the crescents were extra-cellular and applied only to the surface of the red cells.

Also, Sinton [34], by shrivelling erythrocytes with hypertonic saline and swelling them with hypotonic, believes that he has seen the parasites in the various extra-corpuscular positions observed by Rowley-Lawson.

The question as to whether or not the parasite is extra-cellular during most of its life in the human body is interesting from the point of view of treatment. If the extra-corpuscular theory is correct, then the parasite, from the injection of the sporozoite by the mosquito throughout the whole of the schizogony cycle, and during that part of the sporogony cycle up to the formation of the gametocytes, is exposed to the action of quinine circulating in the blood; whilst if the view of the majority is the correct one, the parasite can only be affected by quinine during the sporozoite stage, the merozoite stage and the early trophozoite stage, and it is in the merozoite stage that the parasite is generally held to be most susceptible to the action of quinine.
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Therefore it would appear that the weak concentrations of quinine present in the blood during treatment or during a course of prophylactic quinine exercise their lethal or weakening effect on the parasite during the sporozoite, early trophozoite and merozoite stages at least, and if the extra-corpuscle theory is correct throughout the whole of the rest of the life of the parasite in the human host besides.

It follows that our aim should be to maintain in the blood a concentration of quinine sufficient to destroy all parasites directly or indirectly, and to determine the minimum dosage for this purpose. The dose will require to be higher when the number of infected anopheles is high, during epidemic years, and when other measures of protection are ineffective.

The process will be less efficacious if circumstances exist which tend to lower the resistance of the individual, e.g., stress and strain of active service, exposure to climatic extremes. The well-known fact that a mild attack of malaria adequately treated with quinine will often not clear up till the patient retires to bed, is a very good indication that factors other than quinine play their part in the cure of malaria.

Another factor influencing the dosage is the arrival in the station of batches of non-immunes. Their advent in the ordinary way during the malaria season is often the signal for a great intensification of the malaria, and not only the new arrivals, but the old residents suffer. The non-immunes get infected, the percentage of infected anopheles increases, and the degree of immunity in the old residents is now insufficient to protect them. This is well exemplified after the return to the plains stations in India of parties of troops who have been spending part of the hot weather in the hills.

Watson [35] observed the same phenomenon after the arrival of recruits for labour gangs on the estates of Malaya.

Whatever the environmental conditions, the dose should be sufficient not only to prevent the number of parasites rising above the febrile threshold, but, if possible, to destroy all parasites. The exhibition of quinine must be continued for at least ten days after the latest possibility of infection. We may picture the state of affairs when the body defences and quinine in circulation are just sufficient to scotch, but not to exterminate, the infection. Perhaps fresh infections are constantly being superimposed. The schizogony cycle persists for very long periods, but the number of parasites in the blood-stream is kept at a low level.

At the end of the malaria season, no further fresh infections occurring, the continuation of the quinine for ten days may kill off the infection. On the other hand, the infection may persist till some cause reduces the individual's power of destroying parasites, the schizogony cycle flares up, the total number of parasites rises above the febrile threshold and an attack of malaria ensues.

It is often argued that quinine prophylaxis only masks malaria infection and that when the quinine is stopped the mask is removed and an outbreak
of malaria necessarily follows. Such has not been my experience. If the dose has been sufficient to keep an outbreak of malaria in check, and if the course of quinine is continued for ten days or a fortnight after the danger of further infection has ceased, it is maintained that "masked" cases are the exception, not the rule.

Even in individuals taking no quinine it is well known that cases occur where the disease does not manifest itself till long after infection has taken place.

I will quote two cases within my knowledge.

(1) E. C. H. had his first attack of malaria five months after returning to England, following a prolonged spell of residence in India.

(2) S. M. R. A. returned to England from India on February 5, 1931. During six years in India he had kept perfectly fit and had not had a single day's sickness. He was posted to Catterick (Yorks), and later (September, 1931) developed a typical attack of malaria B.T. He had a rigor on September 6, 1931, followed by another on September 8, 1931, when B.T. parasites were found in the blood. The condition rapidly responded to treatment with quinine.

The question of susceptibility to infection is very imperfectly understood. Some individuals appear to be immune; whether mosquitoes will not bite them, or whether actual resistance to infection exists, is hard to say. I know of one officer (R. T. H.) who slept outside without a net or any other protection in an area where it was impossible for the ordinary individual to sit in comfort after dark. He stated he was never bitten. Another officer (J. N.) had been stationed in many intensely malarious parts of India over a period of seventeen years, and had escaped infection, though he took no precautions against malaria. His resistance against other diseases and his general physique were poor, but repeated and thorough investigation failed to show any trace of malaria.

A further difficulty is the fact that a proportion of any group to whom quinine is given will not absorb the drug in the form usually given, i.e., the sulphate, for it is well known that cases of malaria will frequently react to the bihydrochloride after treatment with sulphate has failed.

It is also necessary to ensure the efficient action of the liver by occasional sharp purges. Otherwise, in many cases, the quinine administered may not be fully absorbed.

Another drawback put forward against the use of quinine prophylaxis is that there is the possibility of producing an immunity to quinine on the part of the parasites, so that the action of quinine when required in curative doses is reduced or lost. The evidence, however, that quinine-fast parasites are produced by the prolonged administration of quinine when given either as a prophylactic or curative is far from being convincing, and Acton [36] and his colleagues of the Dagshai Malaria Hospital are of opinion that the parasites do not become quinine-resistant.

Much has been written of the so-called dangers of quinine administra-
tion. It is well known that in large doses quinine depresses the heart, lowers the blood-pressure and causes depression of the nervous system with a sense of misery and dejection. Atrophy of the optic nerve may follow. In a few particularly susceptible individuals, quinine may produce severe symptoms, e.g., haemoglobinuria, skin eruptions and severe abdominal colic. Such cases are extremely rare, however, when we consider how much quinine is consumed (the annual consumption in India is about 160,000 pounds) [37]. It has even been said that quinine is the cause of blackwater fever. Veretas (Greece, 1858) originated the theory, and Tomaselli (Italy) and Koch later supported it. Much harm was done before this view was discountenanced, and it is now known that blackwater fever may develop without the previous administration of quinine.

I have never seen any serious ill-effects following the use of quinine in the ordinary doses required for treatment, viz., twenty-four to thirty grains a day, and in the course of his large experience Sir Malcolm Watson [38] has only seen one case of idiosyncrasy.

Cinchonism does not persist for more than a few days, and in cases of indigestion a change of salt or an increase in the dosage usually cures the condition.

Quinine, however, is admittedly an unpleasant drug to take, and care must be exercised in choosing the best time and the most suitable method of administration in order to minimize its effects. Largely also on account of its taste it is unpopular, and in dealing with large groups the closest supervision is required to ensure its consumption, for otherwise results will be disappointing. A soldier has been known to place a sponge in his mouth to soak up the quinine he was supposed to swallow.

The supervision required must extend to the preparation of the drug, and frequent examination must be made to ensure that the dose ordered is actually being administered. A solution labelled as containing ten grains to the ounce has been shown to contain only one grain [39], and quinine tablets have been found undissolved in the stools. In cases of doubt the urine should be examined for the presence of quinine.

(To be continued.)